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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,714	02/28/2002	Daphna Havkin-Frenkel	DMCI-0099	7483

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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	PAPER NUMBER
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/087,714	HAVKIN-FRENKEL ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006 and 20 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,19-25 and 30-36* is/are pending in the application.

4a) Of the above claim(s) *30,31 and 33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's submissions filed on May 24, 2006 and November 20, 2006 have been entered.

Claims 1-15, 17-18 and 26-29 are cancelled.

Claims 30-31 and 33-36 are withdrawn.

Claim 32 is withdrawn currently amended.

Claims 16, 19-25 and 30-36 are pending.

Claims 16 and 19-25 are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Election/Restrictions

Applicants respectfully request reconsideration of the withdrawal of previously presented claims 32-36, as the preamble, apparently being used to limit the claims in the prior restriction requirement, is the source of problems in the prosecution. In the alternative, if the arguments above are not found persuasive, Applicants respectfully request that the Examiner allow the Applicants to shift the invention notwithstanding the previous restriction, as it is clear that Claims 32-36 are directed to a method of expressing the chain shortening enzyme in a plant cell. In this regard Applicants point to MPEP 819.01 which states that the Examiner may allow such a shift where the shift results in no additional work or expense, and particularly where the shift reduces work as by simplifying the issues. Applicants maintain that Based on the prior art

searching already performed, these claims are believed free of the prior art, and moreover, it is plain that they remove the enablement issue from the case because they no longer state a preamble of improving Vanillin production or the like. (reply page 7)

Applicants' arguments are unpersuasive, as newly submitted claims 32-36 encompass methods wherein the enzyme is expressed without regard to improving vanillin production, and in any plant cell of any plant species, including heterologous plant cells from *Arabidopsis thaliana* and *Agrostis palustris*, whereas the elected invention is limited to methods wherein overproduction of the enzyme in the homologous species *Vanilla planifolia* improves vanillin production. Such a shift does result in additional work and expense, as the transformation of heterologous plant cells, including plant cells from *Arabidopsis thaliana* and *Agrostis palustris*, and the expression of the 4-hydroxybenzaldehyde synthase of SEQ ID NO:2 therein, must also be searched and considered. Furthermore, since the transformation of heterologous plant cells, including plant cells from *Arabidopsis thaliana* and *Agrostis palustris*, and the expression of the 4-hydroxybenzaldehyde synthase of SEQ ID NO:2 therein, has not been searched and considered, it has not yet been determined whether the withdrawn claims are free of the prior art or enabled.

Claim Rejections - 35 USC § 112

Claims 16 and 19-25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention, for the reasons of record.

Applicants' arguments filed May 24, 2006 have been fully considered but they are not persuasive.

Applicants respectfully assert that maintaining the enablement rejection is improper in this case, as it is unarguable that the specification enables the skilled artisan to physically practice the step of genetically engineering a *Vanilla planifolia* to overproduce an enzyme having the amino acid sequence of SEQ ID NO: 2, or an enzyme encoded by SEQ ID NO: 1. Applicants also maintain that the Office Action has rejected them by apparently interpreting that preamble of the claim to limit the claim, and assert that interpreting the claim to require the absolute increase of vanillin production is improper here. In this regard Applicants point to MPEP 2110.02. Applicants maintain that here, the claim does not breathe life and meaning into the claims, rather, the steps of genetically engineering the *V. planifolia* provide the necessary limitations of the claimed invention. (reply page 5)

With respect to the effect of the preamble on claim interpretation, MPEP 2111.02 also states that "the determination of whether a preamble limits a claim is made on a case-by-case basis in light of the facts in each case; there is no litmus test defining when a preamble limits the scope of a claim." MPEP 2111.02 additionally states that "Any terminology in the preamble that limits the structure of the claimed invention must be treated as a claim limitation.". MPEP 2111.02 additionally states that "The determination of whether preamble recitations are structural limitations can be resolved only on review of the entirety of the application "to gain an understanding of what the inventors actually invented and intended to encompass by the claim.",

and that "During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim."

The Examiner maintains that it is clear from the record that "improving vanillin production in *Vanilla planifolia*" recited in claim 16 is intended to limit the claimed invention.

The disclosure repeatedly emphasizes the improvement of vanillin production in *Vanilla planifolia* as an essential aspect of Applicants' invention.

For example, the abstract states that "Novel compositions and methods for improving vanillin production in cultured *Vanilla planifolia* and in intact plants are provided. Transgenic cells and plants having improved vanillin production are also provided."

The specification at page 1 also states that the field of invention "relates to the field of plant genetic engineering to improve agronomic or commercial properties of plants."

The specification at pages 3-4 additionally states that "it can be seen that improvement of vanillin production, either in tissue culture or in intact plants, would be of significant agronomic and economic advantage. Accordingly, it would be useful to provide means for obtaining high yields of vanillin from cultured cells and tissues and to improve vanillin production in intact vanilla plants. It would also be useful to identify and isolate novel enzymes in the vanillin biosynthetic pathway of *V. planifolia*, and their encoding nucleic acid molecules, for use in enhancing vanillin production in cultured cells or in intact plants."

The specification at page 6 further states that "According to another aspect of the invention, a method for improving vanillin production in *Vanilla planifolia*, is provided, which

comprises genetically engineering the *Vanilla planifolia* to overproduce one or more enzymes associated with one or more steps of vanillin biosynthesis in the *Vanilla planifolia.*" And that " The enzymes preferably are selected from the group consisting of: at least one p-hydroxybenzaldehyde synthase (sometimes referred to as p-coumaric acid chain shortening enzyme, or 4-hydroxybenzaldehyde synthase (4HBS)); at least one cytochrome P450 monooxygenase; and at least one methyl transferase."

The specification at page 7 also states that "In one embodiment of the aforementioned method of improving vanillin production, the genetically engineered *Vanilla planifolia* is a cell or tissue culture. In another embodiment, it is a whole plant. Genetically engineered *Vanilla planifolia* cells or plants produced by the aforementioned method are also provided. These cells or plants preferably produce at least twice as much vanillin as does an equivalent cell which is not comparably genetically engineered."

The specification at page 17 additionally states that "In the present invention, two general approaches are used to improve vanillin production in cultured cells and, in some instances, in intact vanilla plants. The first approach employs manipulation of tissue culture conditions to increase vanillin accumulation in cultured cells. The second approach employs genetic manipulation of the vanillin biosynthetic pathway by up-regulating or down-regulating, as appropriate, enzymes involved in the vanillin biosynthetic pathway or in the conversion of vanillin to vanillyl alcohol."

The specification at page 19 further states "Manipulation of the enzymes involved in the vanillin biosynthetic pathway is another approach used in accordance with this invention to improve vanillin production in vanilla tissue culture and in intact plants."

The specification at page 20 also states "it is believed that up-regulation or some other form of supplementation of p-hydroxybenzaldehyde synthase will enhance vanillin production in cultured cells and in intact plants."

Additionally, pending claims 23 and 25 confirm that "improving vanillin production in *Vanilla planifolia*" recited in claim 16 is intended to limit the claimed invention, because the genetically engineered *Vanilla planifolia* cell of claim 23 and the genetically engineered *Vanilla planifolia* plant of claim 25, which are produced by the method of claim 16, are claimed to produce at "at least twice as much vanillin" as do an equivalent cell or plant which is not genetically engineered.

Applicants also maintain that based on the teachings of the specification and the knowledge in the art, embodied in part by the references provided by the Applicant, the skilled artisan would be convinced that overexpressing the chain-shortening enzymes, e.g. p-hydroxybenzaldehyde synthase, would lead to enhanced vanillin biosynthesis. Applicants respectfully submit that the previously submitted references are completely analogous and would have been meaningful to a skilled artisan confronting the problem the inventors did - i.e. how to improve throughput in a biosynthetic pathway in *V. planifolia*. Applicants maintain that because the precise problem had not been previously faced, they would have looked to references concerning success in other pathways and other plants, and that here, the submitted references teach other pathways involving carbon compounds in other plants - they are not so far afield. (reply pages 6-7)

The Examiner maintains the position that none of the submitted references provides guidance with respect to how to improve the production of vanillin in *Vanilla planifolia* by genetically engineering *Vanilla planifolia* to overproduce an enzyme having the amino acid sequence of SEQ ID NO:2 (a 4-hydroxybenzaldehyde synthase of SEQ ID NO:2 obtained from a *Vanilla planifolia*), and that such guidance is necessary because it is unpredictable whether the overproduction of an enzyme associated with chain shortening of p-coumaric acid to p-hydroxybenzaldehyde would improve the production of vanillin in *Vanilla planifolia*, as the chain shortening of p-coumaric acid to p-hydroxybenzaldehyde is but one of several steps required for vanillin biosynthesis. Improvement of the production of vanillin in *Vanilla planifolia* cells by overexpression of p-hydroxybenzaldehyde synthase would depend not only upon the availability of sufficient p-coumaric acid substrate for the enzyme, but also on the downstream activity of other enzymes required to covert p-hydroxybenzaldehyde product into vanillin, as well as the activity of catabolic enzymes. Given that multiple variables affect the production of vanillin in *Vanilla planifolia*, and given the lack of guidance in the disclosure and in the prior art, it would require undue experimentation for one skilled in the art to determine how to overproduce an enzyme having the amino acid sequence of SEQ ID NO:2 in a manner that would improve the production of vanillin in *Vanilla planifolia*, or in a manner that would produce a *Vanilla planifolia* cell which produces at least twice as much vanillin as a non-genetically engineered cell, as one skilled in the art would have to resort to trial and error experimentation in order to optimize, if possible, multiple variables in order to achieve the desired results.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cynthia Collins
Primary Examiner
Art Unit 1638

CC

Cynthia Collins
2/16/07